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## Citation

Oaklander, Anne Louise. 2011. "Neuropathic Itch." *Seminars in Cutaneous Medicine and Surgery* 30 (2) (June): 87–92. doi:10.1016/j.sder.2011.04.006.

## Published Version

doi:10.1016/j.sder.2011.04.006

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Published in final edited form as:

*Semin Cutan Med Surg.* 2011 June ; 30(2): 87–92. doi:10.1016/j.sder.2011.04.006.

## Neuropathic Itch

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### Abstract

Chronic itch can be caused by dysfunctions of itch-sensing neurons that produce sensory hallucinations of pruritogenic stimuli. The cellular and molecular mechanisms are still unknown. All neurological disease categories have been implicated and neurological causes should be considered for patients with otherwise-unexplained itch. The same neurological illnesses that cause neuropathic pain can also or instead cause itch. These include shingles (particularly of the head or neck), small-fiber polyneuropathies, radiculopathies (e.g., notalgia paresthetica and brachioradial pruritis) and diverse lesions of the trigeminal nerve, root, and central tracts. Central nervous system lesions affecting sensory pathways, including strokes, multiple sclerosis, and cavernous hemangiomas can cause central itch. Neuropathic itch is a potent trigger of reflex and volitional scratching although this provides only fleeting relief. Rare patients whose lesion causes sensory loss as well as neuropathic itch can scratch deeply enough to cause painless self-injury. The most common location is on the face (trigeminal trophic syndrome). Treating neuropathic itch is difficult; antihistamines, corticosteroids, and most pain medications are largely ineffective. Current treatment recommendations include local or systemic administration of inhibitors of neuronal excitability (especially local anesthetics) and barriers to reduce scratching.

Many physicians including neurologists are unaware that neurological problems alone can cause chronic itch. Neuropathic itch and pain are signaling abnormalities – the source of the problem is not where the symptoms are felt. Like neuropathic pain, neuropathic itch is still poorly understood despite fundamental advances in understanding the mechanisms of itch in the normal nervous system.<sup>1</sup> Considered physiologically, neuropathic itch is a pathological form of itch where the stimulus-response curve that governs normal sensation has become distorted and the itch sensation is out of proportion or even completely independent of any pruritogenic stimuli. Like an electrical problem in the wiring harness of an automobile, the actual location and cause of neuropathic itch can be extremely difficult to pin down, but effective treatment may require anatomical and etiological identification of the neurological problem and institution of disease-modifying treatment. In some cases, this may be neurosurgical. Neuropathic itch does not often respond to antihistamines, topical steroids or other medications effective for conventional itch. Furthermore, like other neurological symptoms, itch can signal a potentially serious neurological problem that might need treatment. Most neurology textbooks and training do not discuss the localization and etiology of errant itch, so not all neurological consultations will be insightful. A

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No disclosures or conflicts of interest.

dermatologist should first examine the patient to exclude conventional causes of itch before requesting neurological consultation.

## What causes neuropathic itch?

The anatomical pathways that mediate normal itch sensation were mentioned previously in this issue (see “Anatomy and Neurophysiology of Pruritis”, page XXX). Among somatosensory sensations, itch is the least understood, and the underlying neural circuits are still in the process of being identified. Virtually nothing is known about the cellular and molecular bases of itch under pathological circumstances, so this review is based on fragmentary understanding gleaned from clinical experience and manuscripts largely restricted to case reports. Findings so far suggest that lesions anywhere in the peripheral nervous system (PNS) or central nervous system (CNS) that damage itch-transducing, conducting or processing neurons appear capable of causing neuropathic itch. It is logical to look for the cause of pruritis in the symptomatic area but the causative lesion may be half a meter away in a nerve, nerve root, spinal cord or the brain. Like most other neurological symptoms, what matters is the anatomical location of the lesion, not its etiology. Neuropathic itch has been associated with most of the major categories of neurological disease ranging from stroke, tumors and vascular malformations, to demyelinating disease and radicular compression. This review attempts to summarize the known causes of neuropathic itch, organized by anatomical location.

Like neuropathic pain, only a fraction of patients with these neurological conditions develop chronic itch. It appears that neuropathic itch and pain, like many other chronic conditions, are likely complex conditions in which a specific trigger, neuronal damage, increases risk for symptoms in individuals with underlying susceptibility. There are no data about what the environmental and genetic risk factors for neuropathic itch might be. In the pain field, a fruitful approach has been to screen electronic records for premorbid conditions present prior to the onset of the symptoms.<sup>2</sup> Also unexplained is why a particular illness, zoster for instance, leaves some patients with neuropathic pain, some with neuropathic itch, most with neither, and some with both. At least in some cases, neuropathic pruritis can persist. There are several reports of patients with new self-induced injury decades after strokes or trigeminal surgery when dementia caused their scratching to become uncontrolled.<sup>3,4</sup> In addition to sensing pain and itch, the small-diameter unmyelinated and thinly myelinated axons that carry itch and pain sensation (“small-fibers”) have diverse efferent and trophic actions that are usually related to response to injury. These include microvascular and immune changes (neurogenic inflammation) that may also contribute to itch (e.g., via recruitment of mast cells). These can provide objective evidence that helps identify when itch is neuropathic.<sup>5</sup>

## Painless self-injury from neuropathic itch

The worst complication is self-injury from scratching. Itch patients often develop skin changes from prolonged scratching (e.g. lichenification), but scratching into deeper tissues is virtually pathognomonic for neuropathic itch. For this to develop requires not only intractable itch, but also co-localizing severe sensory loss that renders scratching painless and permits it to continue to the point of self injury. Impaired self-control undoubtedly contributes, although most patients with this are psychiatrically normal. It is nearly impossible to continually resist the urge to scratch a severe chronic itch, and scratching can occur during sleep or at times of inattention. Interestingly, patients and even their physicians may not always understand that their lesions are self-generated.

Painless self-injury from neuropathic itch is far more common on the face than anywhere else on the body. The reasons are unknown, but studying shingles patients showed that

postherpetic itch is far more common after zoster affecting the face than the torso, preliminary evidence of regional variability in susceptibility to neuropathic itch.<sup>6</sup> The face is also unclothed and readily accessible to the fingers; indeed many people engage in absent-minded stereotyped digital facial stimulation (e.g., nose picking, hair twirling), just not to the point of self injury. See the section on facial itch later in this paper for more on trigeminal trophic syndrome (TTS).

## Major neuropathic itch syndromes and how to diagnose them

### Small-fiber polyneuropathy (axonopathy)

It seems appropriate to begin at the skin and proceed proximally. The skin is richly innervated with the small unmyelinated (C-fiber) and thinly myelinated axons (A-delta fibers) that transmit itch and pain sensations (nociception).<sup>7</sup> The term small-fiber polyneuropathy (SFPN) is used for conditions associated with widespread damage or dysfunction of these axons, usually due to systemic or general causes. Some polyneuropathies are highly specific for one particular kind of axon, and itch is specifically associated with neuropathy of the small-diameter axons that transduce and transmit pain and itch. In contrast, sensory neuropathies that predominantly affect the large sensory fibers cause poor balance and loss of touch and joint position sense, and motor axonopathies produce weakness and muscle atrophy. Since itch-fibers are unmyelinated or thinly myelinated, polyneuropathies that damage myelin are unlikely to produce itch as a major symptom. In practice, inflammation and degeneration of a particular axonal subtype often causes varying amounts of “bystander” damage to adjacent axons even if they are not directly targeted. The most common cause of small-fiber polyneuropathy in developed countries is diabetes mellitus, and even pre-diabetes and impaired glucose tolerance.<sup>8</sup> Other important causes include vitamin deficiencies, exposure to toxins including cancer chemotherapy and other medications, and plasma-cell dyscrasias.<sup>9</sup> Identifying and treating these underlying causes is the best way to ameliorate accompanying pruritis.

SFPN usually begins in both feet, innervated by the longest axons, and then the hands typically become involved as symptoms ascend past the knees (Figure 1). Occasional patients present with proximal or diffuse symptoms due to autoimmune attack or other cause of degeneration centered in the sensory ganglia (see below).<sup>10</sup> Diagnosis of SFPN can be difficult because motor signs are absent and standard electrodiagnostic testing (electromyography/nerve conduction study) is insensitive. Normal nerve conduction study results do not preclude a diagnosis of small-fiber neuropathy. The American Academy of Neurology endorses two objective tests for diagnosing SFPN;<sup>11</sup> distal-leg skin biopsies immunolabeled to show the density and morphology of epidermal nerve-fibers (ENF),<sup>12</sup> and autonomic-function testing (AFT), which quantitates cardiovascular responses and sweating.<sup>13</sup> Both tests are available at select academic centers.

Dermatologists are well-qualified to perform skin biopsy for diagnosis of SFPN, but need to know that biopsies need to be taken from a standard site, 10 cm proximal to the lateral malleolus in an area with healthy skin, and they need to be immediately fixed in special fixatives (PLP or Zamboni's) and sent to an academic or commercial laboratory that analyzes such biopsies (these include Johns Hopkins and the Massachusetts General Hospital). Because the punch diameter (usually 3 mm) will figure into calculations of ENF density, punches need to be removed without significantly indenting (stretching) the skin and anesthesia needs to be injected subcutaneously rather than intradermally. The biopsy site should not be sutured and should be covered for 7–10 days. Unlike sural nerve biopsies, skin biopsies can be repeated to monitor disease progression or response to therapy. Biopsies are usually immunolabeled with an antibody against PGP9.5, a pan-axonal marker. This enables

the small sensory nerve endings in the epidermis to be counted with light microscopy. Normative data provide reference ranges.<sup>14</sup>

### **Shingles and other lesions of the neurosensory ganglia**

The spine and skull protect the ganglia from trauma but often cause radicular compression (pinched nerve) when distorted by osteoarthritis. Paraneoplastic syndromes and other autoimmunity (e.g., Sjögren's syndrome) are rare causes of ganglionopathy as well as brachial and lumbosacral plexopathies.<sup>15</sup> By far the most common sensory ganglionitis that causes neuropathic itch is shingles (herpes zoster). The cause is reactivation of endogenous dormant varicella zoster virus and this kills a proportion of sensory neurons.<sup>16</sup> The most common sequel is post-herpetic neuralgia (PHN), which occurs in some 10–15% of cases in unvaccinated patients.<sup>16</sup> PHN is chronic neuropathic pain persisting more than 3 months after the shingles rash resolves; the risk is age-proportional and reduced by vaccination.<sup>17</sup>

There is growing awareness among physicians that chronic post-herpetic itch (PHI) is another potentially disabling consequence of zoster, although many patients have personal awareness of this. PHI and PHN can ensue independently or together after shingles, and with varying relative severities. The most likely assumption (as yet unproven) is that, analogous to PHN, PHI is a system disorder caused by lasting injury to neurons that mediate normal itch sensations. Epidemiological study revealed PHI to be reported by one-third to one-half of shingles patients, and prevalence is greater after shingles on the face or neck than on the torso.<sup>6</sup> It is usually mild or moderate in intensity, but occasional cases with self-injury have been reported in association with severe enough small-fiber loss to render the continued scratching painless.<sup>18</sup> Medications shown effective for PHN may not help PHI, which seems overall more difficult to treat. Opioids are documented effective for PHN, but they often precipitate or worsen itch.<sup>19</sup> PHN is often studied in large clinical trials of new treatments for neuropathic pain designed to meet requirements of the Food and drug Administration. We could learn much about effective therapies by including PHI as an additional outcome.

### **Radicular itch and spinal nerve-root compression (brachioradial pruritis and nostalgia paresthetica)**

Nerve roots are vulnerable to compression and many radiculopathies are traumatic in origin. The hallmark of a radiculopathy is localization of symptoms largely to the body areas innervated by one or more of the nerve roots as they exit the brain and spinal cord; almost always, radiculopathies are unilateral. Neurologists and neurosurgeons have long known about these syndromes and know that patients presenting with radicular patterns of sensory or motor complaints may need spinal imaging and evaluation for decompressive neurosurgery. Other less-common causes of radiculopathy include neoplastic and granulomatous infiltrations, and intrinsic neuropathies that have a predilection for this location, including diabetic truncal radiculopathy (a vasculitis). Self-mutilation of the hand or arm in young children with brachial-plexus injuries sustained at childbirth may be another form of neuropathic radicular itch.<sup>20</sup> Notalgia paresthetica and brachioradial pruritis are dermatological terms that describe one or more focal itchy patches of unknown etiology located on the torso or upper arms respectively. Nerve-root compression from degenerative spine is their most common cause,<sup>21</sup> and it is likely that the other radiculopathies mentioned above cause some of the non-compressive cases.<sup>22</sup>

### **Cranial nerve and root lesions that can cause itch of the throat, jaw, and ear**

Damage to the cranial nerves that contain somatosensory fibers can cause pruritis. Like spinal nerves and roots, cranial nerves can be acutely compressed if they swell (e.g. from viral infection) and chronically compressed by narrowing of the bony foramina from

osteoarthritis and other causes. The trigeminal nerve (V) that innervates most of the face is discussed below, but damage to peripheral or central somatosensory axons of VII, IX, and X can also cause neuropathic itch and pain. Viruses or rare structural lesions can damage peripheral axons, and stroke, multiple sclerosis, and neoplastic, infectious or degenerative diseases cause most central lesions. Radiographic imaging is indicated for new syndromes to identify potential structural causes and lumbar puncture can help identify infectious or autoimmune causes. When neurologists fail to find a lesion, a previous viral infection is often presumed.

The facial nerve (VII) is mostly motor, but it also provides somatosensory innervations to the external surface of the tympanic membrane, the outer ear canal, a piece of skin behind the ear, and part of the cheek anterior to the ear including the tragus via the *nervus intermedius*. This area is variably sized, in some patients including half of the cheek. The glossopharyngeal nerve (IX) carries pain, temperature, and probably also touch from the posterior third of the tongue, the internal surface of the tympanic membrane, and the pinna (external ear). Lesions including zoster can leave chronic pain (glossopharyngeal neuralgia) and or itch (glossopharyngeal pruritis) in the throat or behind the angle of the jaw. The vagus (X) is a primarily motor, parasympathetic and visceral sensory nerve that also transmits pain, touch, and temperature from the larynx, pharynx, part of the pinna, external tympanic membrane, and ear canal, and the meninges of the posterior fossa. Itch sensation is restricted to the mucosa and skin, and is not thought to be present within the body. Some patients with itch from IX or X lesions report a “tickle” in their throat that causes chronic cough, a significant disability.

### **Trigeminal nerve and root lesions that cause facial itch, including trigeminal trophic syndrome**

The only cranial nerve clearly linked to a specific itch syndrome is the trigeminal (V), which innervates most of the face, sinuses, and cranial cavity. Although trigeminal nerve lesions are best known for causing neuropathic pain (trigeminal neuralgia and neuropathy), they also cause chronic itch syndromes. Shingles is a well-known cause, it more often affects the ophthalmic (V<sub>1</sub>) than the maxillary (V<sub>2</sub>) or mandibular (V<sub>3</sub>) divisions. Compression of the intracranial portion of V by an errant blood vessel is increasingly recognized as the most common cause of trigeminal neuralgia. A similar etiology should be considered, particularly in patients with onset at middle age or older. In contrast, onset in patients under 30 years should prompt consideration of multiple sclerosis, particularly in women or when ilateral.

### **Peripheral lesions that can cause central neuropathic itch and trigeminal trophic syndrome (TTS)**

Although most physicians know about trigeminal neuralgia, far fewer know about the corresponding neuropathic itch syndrome, or its major complication, TTS. Throughout the 20<sup>th</sup> century, the major cause of trigeminal itch manifesting as TTS was surgical destruction of the ipsilateral trigeminal (Gasserian) ganglion or its peripheral root to treat trigeminal neuralgia.<sup>23,24</sup> One series reported 18% prevalence of TTS after trigeminal ablation.<sup>25</sup> Before the invention of the first effective medications for neuralgia, carbamazepine and phenytoin, severe trigeminal neuralgia was treated surgically.<sup>26</sup> The combination of dense sensory loss and chronic itch produced a surge in TTS cases. Some patients also had deafferentation pain (*anesthesia dolorosa*). The lesions were first attributed to impaired vitality of deafferented skin from loss of neuronal trophic factors, hence the name. It was only gradually recognized that TTS lesions are self inflicted by scratching, desensate itchy denervated skin. Rare peripheral causes of TTS include compressive skull-base tumors such as meningiomas and acoustic neuromas.<sup>27,28</sup> Neurological evaluation is indicated for all unexplained cases. Rare infectious causes include Herpes simplex and leprosy.<sup>29,30</sup>



TTS can appear anywhere in the trigeminal innervation territory,<sup>18</sup> but is most characteristic at the ipsilateral nasal ala and adjacent cheek and upper lip, in V<sub>2</sub> or V<sub>3</sub> territory (Figure 2). The usual sparing of the tip of the nose is attributed to its innervation by the external nasal branch of the anterior ethmoidal nerve, a branch of V<sub>1</sub>. Most attempts to destroy the trigeminal ganglion or root try to spare V<sub>1</sub>, to prevent blindness from inadvertent trauma to a desensate cornea no longer protected by the blink reflex (neuropathic keratitis).<sup>23</sup> Alternately, the tip of the nose might retain innervation from the intact contralateral nerve.

### **Brain lesions that can cause central neuropathic itch and trigeminal trophic syndrome**

Central causes of neuropathic pain are not as common as peripheral causes. There is no one particular disease that causes central neuropathic itch; it can occur with any disease that affects the ascending pain pathways.<sup>31</sup> Brain lesions reportedly cause 21% of TTS, most often from strokes.<sup>32,33</sup> Less common causes include multiple sclerosis,<sup>34</sup> brain tumors,<sup>35</sup> abscesses,<sup>36</sup> and Sjögren's syndrome.<sup>32</sup> Rare cases have also been attributed to anterior circulation stroke, particularly those that affect the thalamus.<sup>33</sup> Exceptionally rare cases involve syringes or tumors of the medulla or pons.<sup>37</sup> Radiographic imaging of such patients can help identify the central itch pathways.

The Wallenberg or lateral medullary syndrome, which can also cause neuropathic facial pain, is the best-known cause.<sup>38,39</sup> The complete syndrome is caused by infarction of a wedge of lateral medulla, in most cases from vertebral-artery blockage. Occasional cases are attributed to smaller strokes in this same territory, for instance involving the posterior inferior cerebellar artery (PICA),<sup>40,41</sup> or thalamus.<sup>33</sup> The full picture includes signs of abnormality of the vestibular system (vertigo, nystagmus, oscillopsia, vomiting), spinothalamic tract (ipsilateral loss of body pain and temperature), descending sympathetic tract (ipsilateral Horner syndrome) and cranial nerves IX and X (hoarseness and choking), otolith nucleus (double vision), cerebellar connections (ipsilateral ataxia), as well as the descending tract and nucleus of the trigeminal (V) nerve causing loss of pain and temperature on the ipsilateral face. Because the medial sensory pathways are supplied by a different artery, nociceptive sensations (pain and temperature) are damaged but the non-nociceptive sensations (e.g., touch, vibration, proprioception) that ascend in the medial lemniscus and the pyramidal tract carrying motor function are spared. The two sensory pathways converge in the upper brainstem, so more rostral lesions damage all sensory modalities and do not seem likely to cause this syndrome.

### **Spinal-cord lesions**

Spinal-cord injury can combine injuries to both the central axons of peripheral neurons and secondary and tertiary neurons entirely within the CNS. There are only about a dozen reports of intramedullary pruritis, although doubtless many cases go unrecognized. Again, various causative lesions have been described, including trauma causing hemi-body itch as part of the Bown-Séguard syndrome,<sup>42</sup> syringomyelia,<sup>43</sup> and multiple sclerosis.<sup>34</sup> The best documented is intramedullary cavernous hemangioma (cavernoma). These rare congenital malformations comprise less than 5% of all intramedullary lesions. So when we described the third case of neuropathic itch associated with intramedullary cavernoma, we posited a specific association based on their relatively rostro-dorsal location and microscopic pathology.<sup>44</sup> Data from patients with shingles, notalgia, and brachioradial pruritis suggests a rostro-caudal gradient of susceptibility to neuropathic itch.<sup>6</sup> We also suggested that the hemosiderin-laden phagocytes in their rim might be fostering ectopic firing of nearby neurons to make cavernomas highly pruritogenic as well as epileptogenic (when intracranial).<sup>44</sup>

We studied a rat model of spinal-cord injury to further investigate these hypotheses. Microinjecting excitotoxic quisqualate into the dorsal spinal cord of rats produces gliotic cavities like those caused by cavernomas. Some such injected rats begin to scratch and bite at the dermatome on their flank innervated by the damaged spinal-cord segment.<sup>45</sup> Such autotomy develops only in rats whose injection destroys the deep dorsal horn, suggesting such damage may be requisite for developing central spinal itch.<sup>46</sup> The cell bodies of second-order, histamine-triggered itch neurons are in lamina I of the dorsal horn, from there ascending via the contralateral lateral spinothalamic tract to the thalamus.<sup>47</sup> We hypothesized that central itch ensued when these lamina I neurons were preserved but near the lesion and firing excessively due to hemosiderin and gliosis.<sup>46</sup> In these rats, even though the spinal cord was injected, skin biopsies showed profound loss of small-fibers in the skin, so peripheral deafferentation may also contribute.<sup>46</sup>

### Treatment of neuropathic itch

Behavioral treatments are foremost. Surprisingly, patients often do not understand that their scratching is the cause of their skin lesions, and may attribute the itch to the lesions rather than the converse. Explaining the cause of the patients' itch and its potential for self-injury will in many cases be enough to break habitual scratching. However, considerable scratching occurs when patients are asleep or inattentive, so patients with impending or actual ulcers may need to use protective garments to shield their lesions from involuntary scratching. In one patient who scratched through her skull, locking the helmet that she wore to protect her skull defect was the most effective treatment.<sup>18</sup>

Among medications, local anesthetics – whether administered topically, by local injection, or systemically – have proven paramount. These inhibit neuronal firing and affect small-fiber firing at lower doses than required to block motor conduction. High thoracic epidural infusion of bupivacaine and clonidine reportedly helped one patient with V<sub>1</sub> PHN and PHI.<sup>48</sup> There is also limited evidence of efficacy for other inhibitors of action potentials including carbamazepine.<sup>34</sup> Mexiletine, an oral analogue of lidocaine is also reasonable to consider.<sup>49</sup> There are isolated case reports of efficacy of pregabalin,<sup>43</sup>

Some patients with disfiguring facial ulcers and exposed bone require surgical repair,<sup>50</sup> but these will not succeed unless scratching is controlled. Surgical flaps should be well-innervated as well as vascularized. This may require rotation from outside of the affected dermatome, and perhaps from the other side of the face.<sup>51</sup>

### Acknowledgments

Supported in part by the Public Health Service (K24NS059892). Presented in abstract form to the International Federation for the Study of Itch.

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**Figure 1. A patient with chronic itch and scratching-induced lesions on her distal legs** negligible sweat production from the forearm, proximal leg, distal leg and foot sites after iontophoresis of acetylcholine, reflecting dysfunction of her cholinergic sudomotor sweat fibers, consistent with small-fiber polyneuropathy.



**Figure 2. A man with trigeminal trophic syndrome**

This 63-year-old developed left trigeminal itch and pain after left Wallenberg's syndrome (dorsolateral medullary infarction). His trigeminal trophic syndrome (TTS) was maintained by his scratching. Reproduced with permission from Elsevier.<sup>39</sup>